Pulsatile cortisol infusion enhances slow wave sleep and growth hormone secretion in elderly subjects

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Aging is associated with a set of sleep endocrine alterations, notably with a continuous decline of growth hormone (GH) secretion, of slow wave sleep (SWS) and delta power density. Because short-term pulsatile aministration of cortisol increases GH release and SWS in young adults, we wondered whether similar effects can be induced also in elderly men. We studied the effect of pulsatile cortisol infusion (1mg kg^{-1} body weight) or placebo on sleep EEG and GH secretion in 8 healthy elderly subjects (between 60 and 80 years old). Manual sleep-EEG scoring demonstrated a significant increase in SWS (mean ± SD: 12.0 ± 10.4 min. after cortisol vs 6.6 ± 6.4 min. after placebo, $p < 0.05$) and a decrease of REM sleep (38.6 ± 20.2 min. after cortisol vs 67.4 ± 22.5 min. after placebo, $p < 0.05$). Results from power spectral analysis, calculated for nonREM sleep during total night, revealed significant increases in delta power (28.7% ± 18.0%, $p < 0.05$) and in theta power (19.9% ± 20.3%, $p < 0.05$) after cortisol vs placebo. Cortisol infusions increased the GH secretion prior to sleep onset (18.00-23.00 h)(area under curve: 734.7 ± 106.3 ng/ml x min. after cortisol vs 146.6 ± 32.5 ng/ml x min. after placebo, $p < 0.02$), but remained largely unchanged during sleep.
Our data show that sleep EEG and GH release are modulated by cortisol administration in a way similar as in young subjects, however to a lesser extent. The stimulatory effect on both GH release and SWS points to a mechanism involving glucocorticoid-enhanced production and release of GH-releasing hormone that activates pituitary GH release and simultaneously antagonizes the effects of corticotropin-releasing hormone and somatostatin.

Calcium ions in signal transduction: possible target for drug action

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Calcium ions are critically important for many functions of the central nervous system, such as signal transduction and neurotransmitter release. The large difference between intracellular and extracellular calcium ion concentration highlights the importance of the mechanisms controlling influx and efflux of this ion. Thus, loss of regulatory ability of these mechanisms and subsequent altered intracellular calcium levels may be involved in the pathophysiology of several disorders, as suggested for Alzheimer disease and bipolar disorder.

Several of the G-protein- or tyrosine kinase- linked receptors initiate a cascade that generates intracellular inositol-triphosphate (InsP3) followed by an increase in cytosolic free calcium concentration as a consequence of both calcium mobilisation from intracellular stores and activation of calcium influx through plasma membrane. Multiple pathways appear responsible for this calcium influx, as receptor activation or influx activated by depletion of calcium stores. Hence, the different calcium channels are an interesting target for pharmacological intervention.

Transmembrane acid-extrusion mechanisms: a target for neuropsychopharmacological drug design?

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Seizures, alcohol/benzodiazepine-withdrawal and rapid cycling are often attributed to central hyperexcitability. Recently we observed that a moderate decline of *intracellular pH* decreased excitability*. Brain cells balance their acidic pH by physico-chemical buffering, metabolism and *transmembrane acid extrusion*. In the present *in vitro*-study we examined the effects of *inhibitors of transmembrane acid extrusion mechanisms* (**IAE**, dominated by several isoforms of Na^+/H^+- and Cl^-/HCO_3^--antiports in neurons) on central excitability. Intracellular recordings were carried out in CA3-neurons (hippocampal slice). Hyperexcitability, characterized by epileptiform discharges (**ED**), was induced by bicuculline, caffeine or low magnesium in the superfusing bath solutions. The added inhibitors of Na^+/H^+-exchangers, amiloride and harmaline, reversibly suppressed ED at exposure times of >30min. This effect is similiar to the specific blocker of Na^+/H^+-isoform1 (HOE 642) and to inhibitors of Cl^-/HCO_3^--exchange (DIDS/SITS) system. Our results demonstrate a potent inhibitory action of IAE (0.1-0.5mM, n=29) on hyperexcited central neurons. However, further research is needed to identify the essential subtypes of neuronal acid extrusion for specific drug design. Alltogether, the modulation of transmembrane acid extrusion represents a promissing target for the development of a new class of neuropsychopharmaca.

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Negative symptoms in affective, schizoaffective and schizophrenic disorders 15 years after the onset of illness

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Negative symptoms were widely accepted as core symptoms of schizophrenia. However, there is a increasing controversy about negative symptoms in terms of specificity, reliability of assessment and the concept (wide or narrow). Some research groups have found negative symptoms not only in schizophrenic but also in affective, neurotic and somatic disorders. The distinction of negative symptoms in primary, enduring and secondary, nonenduring negative symptoms was proposed, because of the clear overlap with symptoms of depression, neuroleptic-induced side-effects or psychological effects of environmental deprivation. But clinical distinguishing of primary versus secondary negative symptoms seems to be of potential low reliability.

In our study we compared the course of negative symptoms in patients with affective, schizoaffective and schizophrenic disorders over a period of 15 years. All patients had their first episode of mental illness in the period from 1980 to 1982 and were admitted in the psychiatric hospital of the LMU, Munich. Negative symptoms were assessed with different rating scales (BPRS, PANS, SANS, NAMDP). The three negative symptoms -affective flattening, alogia and avolition-, that were included in the diagnostic criteria (DSM-IV, ICD-10) were differentially considered. In order to delineate primary from secondary negative symptoms, ratingscales for extrapyramidal side effects, medication and sociodemographic data, were additionally ascertained.